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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 29

Application Number: 08/931,219
Filing Date: September 16, 1997
Appellant(s): Falo & Rock

Diane R. Meyers
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed February 15, 2000 (Paper No. 28).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct. See Summary of the Invention at pages 5-9 of the specification.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

The rejection of claims 1-3, 5-17, 19-32, 34-47, and 49-61 under 35 U.S.C. § 112, first paragraph, as being enabled for the breadth of the claimed invention, the enabled breadth being the claimed methods which are limited to biolistic approach into skin, direct injection into skin, or by subcutaneous injection.

The rejection of claims 1-3, 5-17, 19-32, 34-47, and 49-61 under 35 U.S.C. § 112, second paragraph, has been withdrawn in view of appellant's arguments.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because appellant fails to argue that their disclosed grouping of the claims are separately patentable over each other. While appellant asserts separately patentable groupings of the claims, all of the claims are argued together under each grounds of rejection. 37 CFR 1.192(c)(7) requires the inclusion of reasons in order to avoid unsupported assertions of separate patentability.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior or Post-Filing Art of Record

The following is a listing of the **prior art** of record relied upon in the rejection of claims under appeal.

Tang et al. "Genetic Immunization is a Simple Method for Eliciting an Immune Response." Nature, Vol. 356, No. 6365 (March 12, 1992), pp. 152-154.

Barry et al. "Production of Monoclonal Antibodies by Genetic Immunization." Biotechniques, Vol. 16, No. 4 (April 1994), pp. 616-618.

Hui et al. "Generation of Allo-Reactive Cytotoxic T Lymphocytes by Particle Bombardment-Mediated Gene Transfer." Journal of Immunological Methods, Vol. 171, No. 2 (May 16, 1994), pp. 147-155.

5,593,972 WEINER et al. 1-14-1997

The following is a listing of **post-filing** art of record (published after appellant's effective filing date), but relied upon in the enablement rejection of claims under appeal. Barry et al. "Biological Features of Genetic Immunization." Vaccine, Vol. 15, No. 8, (1997), pp. 788-791.

(10) New Prior or Post-Filing Art

Fundamental Immunology, William E. Paul, Raven Press: New York, Third Edition (1993), pages 121 and 593. (Cited to set forth immunological facts in response to appellant's assertions in art rejections).

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. §112, first paragraph:

Claims 1-3, 5-17, 19-32, 34-47, 49-61, and 63-71, on appeal, stand rejected under 35 U.S.C.§112, first paragraph, because the specification fails to provide an enabling disclosure for the breadth of the claimed invention. Please note that appellant's arguments are partially persuasive. As such, this rejection is maintained with regard to only one aspect of the rejection of record advanced on pages 2-3 of the prior Office action mailed June 6, 1999 (Paper No. 23). Specifically, the specification, while being enabling for methods of treating a mammalian host capable of generating an immune response, comprising production of the

particulate polynucleotide which comprises a DNA on its surface, wherein said DNA fragment encodes an antigen of interest, and inoculating the host with the particulate polynucleotide by the **biolistic approach into skin, direct injection into skin, or by subcutaneous injection** (including subcutaneous injection of antigen presenting cells transfected with the particulate polynucleotides), so that the particulate polynucleotide is delivered to the cytoplasm of an antigen presenting cell such that said antigen of interest is presented to the membrane surface of the antigen presenting cell by MHC class I, does not reasonably provide enablement for the claimed methods encompassing **any and all** routes of administration of the particulate polynucleotide or of the antigen presenting cells transfected with the particulate polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-3, 5-17, 19-32. 34-47, 49-61, and 63-71, in general, are directed to methods of treating by eliciting an immune response in a host through the delivery of particulate polynucleotides coated with DNA fragments encoding antigenic proteins or antigenic protein fragments. The claims require that delivery be to the cytoplasm of an antigen presenting cell within the host (*in vivo* administration), or delivery to the host of an antigen presenting cell modified with the particulate polynucleotide (*ex vivo* administration) such that presentation of the antigen elicits an anti-tumor or anti-viral immune response that destroys neoplastic or virally infected cells.

It is initially noted that appellant's broad claims read on any route of administration of the particulate polynucleotide comprising on its surface a DNA encoding an antigen of interest (or of the antigen presenting cells transfected with the particulate polynucleotides). However, the specification fails to teach or provide sufficient guidance for routes of administration other than into skin or the subcutaneum. It is well known that the skin tissue (epidermis) is prevalent with dendritic cells (see specification page 6, lines 25-27), *i.e.*, antigen presenting cells, note that dendritic cells are also termed Langerhans cells). See also a publication submitted by appellant in Exhibit II of Paper No. 11, (Condon et al., Nature Medicine, Vol. 2, (1996)) at page 1122, column 2, paragraph 2, wherein Condon et al. support that skin tissue is prevalent with dendritic cells. As such, any other route of administration would require targeting to the antigen presenting cell (*e.g.*, intramuscular, and intravascular routes of administration have not been shown by the art or by the specification to be sufficient for targeting antigen presenting cells). The specification fails to teach or provide sufficient guidance with regard to cell-targeting to dendritic or other antigen presenting cells (such as B-cells) not located in skin or the subcutaneum or located in the skin but targeted by some mode of delivery other than biolistic injection into skin or the direct injection into subcutaneum, for example. Please note that the direct injection is interpreted as it encompasses both gene gun injection (the biolistic approach) as well as by a needle without gene gun delivery.

Note that all claims require use of a particulate polynucleotide for genetic immunization. It is well known in the genetic immunization art that little is known about the

biology underlying its effectiveness. See page 788, column 2, 1st paragraph, Barry et al. (Vaccine, 1997). See also Condon et al. at page 1122, column 1, 3rd paragraph, who similarly report that the mechanism of genetic immunization is unknown. With relevance to the instant application, Barry et al. compare efficiency of genetic vaccination by intramuscular (i.m.) injection vs. gene gun into the epidermis (skin) and conclude that gene gun is more effective for eliciting an immune response per unit DNA. See page 791, last paragraph. While Barry et al. support i.m. injection of larger amounts of naked DNA (see page 791, last paragraph), Barry et al. fail to support that i.m. injection (or any other route of administration) of particulate polynucleotides (as recited in the claims) would result in delivery to antigen presenting cells such that presentation causes an MHC class I immune response (as recited in the claims), particularly since it is unclear, due to the ambiguity of the genetic immunization art, if sufficient antigen presenting cells are present in muscle tissue (or in the vasculature) to induce an MHC class I immune response by presentation of antigen to the antigen presenting cell (an embodiment specifically recited in the claims. As such, without evidence to the contrary indicating that the particulate polynucleotides (as recited in the claims) would be efficiently delivered without use of the biolistic approach into skin or direct injection into the subcutaneum, it is maintained that the claimed methods are only enabled for gene gune delivery (biolistic approach) into skin or direct injection into the subcutaneum, and are not enabled for any other routes of administration, particularly since dendritic cells are most prevalent in skin tissue.

35 U.S.C. §102(b):

Claims 1, 15, 29, 68, 69 and 71, on appeal, stand rejected under 35 U.S.C. §102(b) as being anticipated by either Tang et al. (Nature, 1992) or Barry et al. (Biotechniques, 1994).

Note that claim 70 has been withdrawn from this rejection as the cited references do not specifically teach *in vitro* delivery of the particulate polynucleotide to an antigen presenting cell.

It is initially noted that Tang et al. teach each and every step of the claimed methods such that any effect of following those steps would be an inherent effect, and thus, such an effect would not need to be specifically addressed in the teachings of Tang et al. Specifically, Tang et al. teach the direct injection by use of the biolistic approach into skin of the ear of a mouse microparticles coated with DNA encoding human growth hormone, and with DNA encoding α-1 antitrypsin. See page 152, column 1, first paragraph, and page 154, column 1, 2nd paragraph. Tang et al. teach the production of antibodies as a result of following their method of genetic immunization. See page 154, column 1, 2nd paragraph. Note that the claims are not limited to any specific antigen, nor is MHC class I restricted to CTL-mediated responses as antigen processing and presentation via MHC class I can initiate a variety of immune responses which would also encompass the generation of antibodies. In some cases, antibodies can be involved in inducing cell-killing of virally infected cells. Again, note that it is the Examiner's position that any effect of the method steps is inherent, however, Tang et al. do discuss how the generation of antibodies by genetic immunization in animals could guard

against pathogenic infection by producing foreign antigens in restricted subsets of self-cells that mimic natural infections. See page 154, column 2. As such, it is maintained that the methods of Tang et al. meet all of the limitations of the claims in that each and every step recited in the claims is taught by Tang et al., and any effect by following each step taught by Tang et al. is an inherent effect. Thus, Tang et al. anticipate claims 1, 15, 29, 68, 69, and 71. Note that the term "direct injection" is interpreted as encompassing both direct injection using a gene-gun as well as direct injection without use of a gene-gun. As such, Tang et al. meet the limitation "direct injection" in all of the claims included under this rejection, since Tang et al. teach direct injection into skin by use of a gene gun.

Similarly, Barry et al. teach each and every step of the claimed methods. Barry et al. teach direct injection into skin of the ear of a mouse using the biolistic approach, a particle coated with DNA encoding human growth hormone. Barry et al. teach the production of antibodies as a result of inoculation with DNA encoding human growth hormone. See page 1, column 2. Note that the claims are not limited to any specific antigen, nor is MHC class I restricted to CTL-mediated responses as antigen processing and presentation via MHC class I can initiate a variety of immune responses which would also encompass the generation of antibodies. In some cases, antibodies can be involved in inducing cell-killing of virally infected cells. Again, note that it is the Examiner's position that any effect of the method steps is inherent. As such, it is maintained that the methods of Barry et al. meet all of the limitations of the claims in that each and every step recited in the claims is taught by Barry et

al., and any effect by following each step taught by Barry et al. is an inherent effect. Thus, Barry et al. anticipate claims 1, 15, 29, 68, 69, and 71. Note that the term "direct injection" is interpreted as encompassing both direct injection using a gene-gun as well as direct injection without use of a gene-gun. As such, Barry et al. meet the limitation "direct injection" in all of the claims included under this rejection, since Barry et al. teach direct injection into skin by use of a gene gun.

35 U.S.C. §102(b):

Claims 1, 15, 29, and 68-71, on appeal, stand rejected under 35 U.S.C. §102(b) as being anticipated by Hui et al. (Journal of Immunological Methods, 1994).

Note also that a Medline print-out of the complete citation of Hui et al. has been provided for the benefit of appellant to demonstrate that the cited reference has a 102(b) relevant date of May 16, 1994. The effective filing date of the instant application is September 28, 1995, over one year after the publication of the cited reference, Hui et al.

Hui et al. teach each and every step of the claimed methods. Hui et al. teach the direct injection into mouse spleen (*in situ*-by peeling back the skin to expose the spleen, see Materials and Methods, Section 2.5) by use of the biolistic approach, DNA encoding H-2k^b. Hui et al. teach that the particles injected by gene-gun penetrated up to several cell layers within spleens which were immunized under optimal conditions. See Results, Section 3.3, sentence bridging columns 1 & 2. Hui et al. report that the immunized spleen cells gave a 3-4 fold increase in

the anti-H-2k^b CTL response compared to non-immunized control mice. See page 154, column 2, first paragraph, and Table 4. Hui et al. go on to report the transformation of animal tissue cell culture using the same apparatus. See page 154, column 2, first paragraph. Note that the claims are not limited to a specific antigen, or any particular route of administration by the biolistic approach. Again, note that it is the Examiner's position that any effect of following the method steps of Hui et al. is inherent. As such, it is maintained that the methods of Hui et al. meet all of the limitations of the claims in that each and every step recited in the claims is taught by Hui et al., and any effect by following each step taught by Hui et al. is an inherent effect. Thus, Hui et al. anticipate claims 1, 15, 29, and 68-71. Note that the term "direct injection" is interpreted as encompassing both direct injection using a gene-gun as well as direct injection without use of a gene-gun. As such, Hui et al. meet the limitation "direct injection" in all of the claims included under this rejection, since Hui et al. teach direct injection into mouse spleen by use of a gene gun.

With regard to the gene-gun approach into spleen cells, it is noted that consultation of an Immunology text (Fundamental Immunology by William Paul) indicates that the spleen contains a sufficient amount of antigen processing cells as the dendritic cells of the spleen process and present protein antigen effectively. Specifically, isolated (DCs) dendritic cells of the spleen have been found to be highly active as both stimulator cells in the MLR (mixed leukocyte reaction) and effective APCs (antigen presenting cells) in initiating CD8 cytotoxic responses in primary antibody responses and in presentation of antigens to CD4 T cells. See

page 121, column 1, 2nd paragraph. Note that a copy of this page of the Text is provided to represent routine knowledge in the immunology art.

35 U.S.C. §103:

Claims 1-3, 5-17, 19-32, 34-47, 49-61, and 63-71, on appeal, stand rejected under 35 U.S.C. §103 as being unpatentable over Weiner et al. (US Patent 5,593,972) taken with either Tang et al. (Nature, 1992) or Barry et al. (Biotechniques, 1994).

Weiner et al. teach methods of genetic vaccination using DNA encoding target antigens of interest. Weiner et al. teach target antigens of interest for use in genetic immunization against tumors, and viral and bacterial pathogens (*e.g.*,HIV gp160 and human neu oncogene). Weiner et al. teach the use of mouse models designed by using tumor cells that specifically express a foreign target protein of interest. See Examples 1-47 and Tables 1 & 2, for example. Weiner et al. discuss that the mechanism of action behind the immune response elicited by the target antigen involves antigen presentation which in turn stimulates CTL response. See column 8, lines 37-51. In fact, here, Weiner et al. report their observations that their genetic immunization protocol is more likely to elicit CTL response than other methods of immunization known in the art. See column 8, lines 48-51. Weiner et al. go on to report their results supporting a broader, more effective immune response which was capable, by virtue of CTL's, of completely eliminating tumors. See column 27, Example 2, lines 1-47. Note that Weiner et al. used tumor mouse models which did not involve intramuscular

injection, as the tumor cells were transfected *ex vivo* and then implanted subcutaneously into the mouse model to show some level of protection against tumor growth by virtue of a CTL response. See Example 2. Weiner discuss and demonstrate that their methods entail *in vivo* or *ex vivo* administration of the genetic vaccine. Weiner et al. specifically teach direct injection of the genetic vaccines into muscle of mice, however also specifically discuss the use of a needleless injection device for simultaneous administration of the genetic vaccine intramuscularly, intradermally, and subcutaneously. See column 20, lines 27-31. Weiner et al. differ from the claimed invention in that they do not specifically teach the use of particulate polynucleotides comprising the DNA vaccine on its surface, rather Weiner et al. teach the use of plasmid DNA vaccines. Weiner et al. also differ from some of the claims in that they do not specifically teach the use of the biolistic approach for administration of the DNA vaccines. However, at the time the claimed invention was made, Weiner et al. suggest and discuss the application of the biolistic approach to their methods of genetic immunization. See column 20, lines 32-36, for example. Weiner et al. go on to discuss that an increase in efficiency of the immune response (as compared to that seen with intramuscular injection) may be achieved by use of a direct DNA delivery system such as particle bombardment. See column 32, lines 55-57. As such, at the time the claimed invention was made, it was routine knowledge in the genetic immunization art to deliver DNA encoding target antigens of interest by means of particle bombardment. This observation is represented by the teachings of either Tang et al. or Barry et al.

Tang et al. teach the direct injection by use of the biolistic approach into skin of the ear of a mouse microparticles coated with DNA encoding human growth hormone, and with DNA encoding α-1 antitrypsin. See page 152, column 1, first paragraph, and page 154, column 1, 2nd paragraph. Barry et al. teach direct injection into skin of the ear of a mouse using the biolistic approach, a particle coated with DNA encoding human growth hormone. See page 1, column 2.

Accordingly, in view of the routine knowledge of the biolistic approach as applied to the art of genetic immunization as represented by the teachings of either Tang et al. or Barry et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made to modify the genetic immunization protocol of Weiner et al. by applying particle bombardment rather than direct injection. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, particularly since Weiner et al. suggest the result of the use of particle bombardment would be an increase in the efficiency of the immune response generated by genetic immunization.

Thus, it is maintained that the claimed invention is *prima facie* obvious in the absence of evidence to the contrary.

(12) New Ground of Rejection

This examiner's answer does not contain any new ground of rejection.

(13) Response to Argument

As Applied to the Rejection Under 35 U.S.C. § 112, First Paragraph:

Please note that appellant's arguments are partially persuasive. As such, this rejection is maintained with regard to only one aspect of the rejection of record advanced on pages 2-3 of the prior Office action mailed June 6, 1999 (Paper No. 23). Specifically, it is held that the specification is enabling for methods of treating a mammalian host capable of generating an immune response, comprising production of the particulate polynucleotide which comprises a DNA on its surface, wherein said DNA fragment encodes an antigen of interest, and inoculating the host with the particulate polynucleotide by the **biolistic approach into skin, direct injection into skin, or by subcutaneous injection** (including subcutaneous injection of antigen presenting cells transfected with the particulate polynucleotides), so that the particulate polynucleotide is delivered to the cytoplasm of an antigen presenting cell such that said antigen of interest is presented to the membrane surface of the antgen presenting cell by MHC class I.

Appellant argues on page 4 of the Brief that direct injection is enabled to points other than the skin and point to Example 7 of the specification which demonstrates subcutaneous injection of the particulate polynucleotide. As such, while the enabled claimed breadth is drawn to direct injection into skin as well as subcutaneous injection of the particulate polynucleotides, it is maintained that points other than skin tissue or the subcutaneous tissue would not provide the intended (and recited) claimed effect drawn to presentation by an antigen presenting cells by the MHC class I pathway. This is because the specification fails to teach or provide sufficient guidance for routes of administration of particulate polynucleotides

other than into skin or the subcutaneum. It is well known that the skin tissue (epidermis) is prevalent with dendritic cells (antigen presenting cells) (see page 1122, column 2, paragraph 2 of Condon et al., Nature Medicine, 1996) such that any other route of administration would require targeting of the particulate polynucleotides to the antigen presenting cell (*e.g.*, intramuscular, and intravascular routes of administration have not been shown by the art or by the specification to be sufficient for targeting particles coated with DNA to antigen presenting cells). The specification fails to teach or provide sufficient guidance with regard to cell-targeting to dendritic or other antigen presenting cells (such as B-cells) not located in skin or the subcutaneum or located in the skin but targeted by some mode of delivery other than biolistic injection into skin or the direct injection into subcutaneum, for example. Please note that the direct injection is interpreted as it encompasses both gene gun injection (the biolistic approach) as well as by a needle without gene gun delivery.

Note that all claims require use of a particulate polynucleotide for genetic immunization. It is well known in the genetic immunization art that little is known about the biology underlying its effectiveness. See page 788, column 2, 1st paragraph, Barry et al. (Vaccine, 1997). (See also Condon et al. at page 1122, column 1, 3rd paragraph, who similarly report that the mechanism of genetic immunization is unknown.) With relevance to the instant application, Barry et al. compare efficiency of genetic vaccination by intramuscular (i.m.) injection vs. gene gun into the epidermis (skin) and conclude that gene gun is more effective for eliciting an immune response per unit DNA. See page 791, last paragraph.

While Barry et al. support i.m. injection of larger amounts of naked DNA (see page 791, last paragraph), Barry et al. fail to support that i.m. injection (or any other route of administration) of a particulate polynucleotide (as recited in the claims) would result in delivery to antigen presenting cells such that presentation causes an MHC class I immune response (as recited in the claims), particularly since it is unclear, due to the ambiguity of the genetic immunization art, if sufficient antigen presenting cells are present in muscle tissue (or in the vasculature) to induce an MHC class I immune response by presentation of antigen to the antigen presenting cell (an embodiment specifically recited in the claims). As such, without evidence to the contrary indicating that the particulate polynucleotides (as recited in the claims) would be efficiently delivered without use of the biolistic approach into skin or direct injection into the subcutaneum, it is maintained that the claimed methods are only enabled for gene gune delivery (biolistic approach) into skin or direct injection into the subcutaneum, and are not enabled for any other routes of administration, particularly since dendritic cells are most prevalent in skin tissue, more particularly since the claims require delivery of particulate polynucleotides and the specification fails to teach a representative number of tissue points which comprise sufficient numbers of antigen presenting cells which take up the DNA coated on the particle surface such that MHC class I is activated.

It is maintained, in view of the lack of showing or guidance for any and all routes of administration of the particulate polynucleotide, that the cited post-filing art of record (Barry et al.) clearly indicates an unpredictable as well as undeveloped status of the genetic

immunization art. See page 788, column 2, 1st paragraph, Barry et al. (Vaccine, 1997). Case law has established that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). To this end, case law has established that in terms of predictability, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof, In re Marzocchi , 439 F.2d 220, 223 - 24, 169 USPQ 367, 368 - 70 (CCPA 1971). Thus, what is known in the art provides evidence as to the question of predictability, and as discussed, none of the cited post-filing art of record provide a prediction of cell-targeting to antigen presenting cells by routes of administration other than gene gun into skin, direct injection into skin, and direct injection into the subcutaneum of the particulate polynucleotide. Furthermore, see Hybritech Inc. v. Monoclonal Antibodies, Inc., where the courts have stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). **However,** that general, oft-repeated statement is merely a rule of supplementation, **not** a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. **However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute**

adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Furthermore, with regard to the enablement standard and what is required under enablement, appellant must provide objective enablement to practice the claimed methods. The determination of objective enablement is based on the following factors: the quantity of experimentation necessary to practice the claimed methods as broadly claimed, the amount of direction and/or guidance provided by the specification, the absence of working examples for the demonstration or reasonable correlation to any and all routes of administration which would effectively target the particulate polynucleotides to a sufficient number of antigen presenting cells, and the unpredictable and undeveloped state of the art of genetic immunization as supported by the cited post-filing art of record, in particular at the time of filing, and more particularly with respect to the breadth of the claims directed to any and all routes of administration of the particulate polynucleotides such that the encoded antigen would be presented and MHC class I activated (as recited in claims). As such, it is maintained that appellant's have not provided objective enablement which corresponds to the necessary guidance and direction for the skilled artisan to make and use the claimed invention.

Therefore, for the reasons presented above and in the "Ground of Rejection", the Examiner maintains the rejection under 35 U.S.C. §112, first paragraph.

As Applied to the Rejection Under 35 U.S.C. § 102(b)-Tang et al. or Barry et al.:

On page 6 of the Brief, appellant argues that the claims recite elicitation of an immune response, particularly an anti-tumor or anti-viral immune response that destroys neoplastic or virally infected cells, the immune response being through the MHC class I pathway. Appellant continues that the skilled artisan would recognize that presentation via MHC class I results in elicitation of a CTL response. As such, appellant argues that it would be apparent to the skilled artisan that appellant is claiming a different response than that taught by either Tang or Barry as both references teach an antibody response. Appellant argues that the mechanism by which an antibody response is triggered is different from that by which a CTL response is elicited in that antibody responses are not related to class I presentation and rather require class II presentation to helper T cells, not to CTLs, and further require that the presented protein be recognized by B cells. Appellant goes on to argue that targeting the delivery of DNA to the cytoplasm of (APCs) antigen presenting cells according to the present invention is not taught by the cited references. Appellant asserts that antibody responses are not generally effective against tumor cells or virally infected cells as are appellant's claimed methods. Thus, appellant concludes that the methods of Tang and Barry teach a different route of action and a different result as compared to the claimed methods.

In response, it is maintained that each of the cited references of record (Tang et al. and Barry et al.) teach each and every step of the claimed methods and thus, any effect, is inherent to carrying out the method, so long as there is no manipulative difference in the steps. Such inherency does not require a specific teaching of the intended effect by the cited references.

Case law has established that in a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Appellant's arguments are directed to an alleged difference in the mechanism of action as a result of an alleged different route of action. However, both Tang et al. and Barry et al. teach a method identical to the claimed method, direct injection into the skin of a mouse by the biolistic approach a particle coated with DNA encoding an antigen of interest. As such, the generation of antibodies may have been the disclosed effect of Tang et al. and Barry et al., however, it is held that any other effect (APC presentation by MHC class I which would have led to a variety of immune responses including a CTL immune response) would have been inherent in following the steps of the methods taught by Tang et al. and Barry et al., as these steps are identical to the claimed steps.

In the paragraph bridging pages 6-7 of the Brief, appellant argues that neither Tang or Barry support the Examiner's assertion that antigen processing and presentation via MHC class I can initiate a variety of immune reactions which would also encompass the generation of antibodies.

In response, it is noted that the Examiner's assertion is an immunological fact. Consultation of the Immunology text, Fundamental Immunology, *supra*, indicates that functional properties of MHC class I include, vigorous graft rejection, potent stimulation of antibody production, cell-mediated lympholysis reactions, MHC restriction of effector T cells

reacting against a variety of endogenous antigens presented on cell surfaces, presentation of endogenous peptide ligands to CD8+ T lymphocytes, most notably CTLs. See page 593, column 2, first paragraph. Note that the claims are not limited to any specific antigen, nor is MHC class I restricted to CTL-mediated responses as explained above. As such, it is the Examiner's position that any effect of the method steps is inherent and because Tang and Barry teach only the measurement of the production of antibodies, this does not exempt the teachings of Tang and Barry as they apply specifically to the claimed method steps, particularly since the production of antibodies is part of the cascade of immune responses as a result of activation of MHC class I. Furthermore,Tang et al. discuss how the generation of antibodies by genetic immunization in animals could guard against pathogenic infection by producing foreign antigens in restricted subsets of self-cells that mimic natural infections. See page 154, column 2. It is maintained, then, that any other MHC class I effect would be inherent in the steps of disclosed methods of Tang and Barry as these methods are identical to the claimed methods.

On page 7 of the Brief, appellant argues that both Tang and Barry teach use of a gene gun or biolistic device, and that claim 29 is specifically directed to direct injection and not a biolistic device. In response, it is noted that the term "direct injection" is interpreted as encompassing both direct injection using a gene-gun as well as direct injection without use of a gene-gun. As such, both Tang et al. and Barry et al. meet the limitation "direct injection" in all of the claims included under this rejection, since both Tang et al. and Barry et al. teach

direct injection into skin by use of a gene gun. There is no limitation recited in claim 29 directed to direct injection without a gene gun or biolistic device.

On page 7 of the Brief, appellant argues that claims 68 and 69 require transfection of APCs (note that claim 70 has been withdrawn from this rejection as indicated in the Grounds of Rejection above), and neither reference teaches such transfection of APCs. In response, again, it is held that the steps of the methods of each of Tang et al. and Barry et al. are identical, as such the effect of transfection of APCs would be inherent in carrying out the disclosed steps of Tang et al. and Barry et al. Furthermore, Tang et al. and Barry et al. teach injection into skin and it is well known in the immunology art that dendritic cells (antigen processing cells) are prevalent in skin tissue. As such, it is an immunologically sound assertion to hold that transfection of antigen presenting cells (in this case, dendritic cells of the skin) is an inherent result of the methods of Tang et al. and Barry et al., the direct injection into the skin of the particle coated with DNA.

Therefore, for the reasons presented above and in the "Ground for Rejection", the Examiner maintains the rejection under 35 U.S.C. § 102.

As Applied to the Rejection Under 35 U.S.C. § 102(b)-Hui et al.:

On page 8 of the Brief, appellant argues that, contrary to the claimed invention, Hui discusses immunization through thigh muscle and spleen cells, not dendritic cells or any other type of APC. Appellant argues that, contrary to the claims, such immunization does not

appear to stimulate a CTL response as Hui only teach that after restimulation *in vitro*, anti-H-$2k^b$ activity was seen.

In response, it is maintained that Hui et al. teach each and every step of the claimed methods. Hui et al. teach the direct injection into mouse spleen (*in situ*-by peeling back the skin to expose the spleen, see Materials and Methods, Section 2.5) by use of the biolistic approach, DNA encoding H-$2k^b$. Hui et al. teach that the particles injected by gene-gun penetrated up to several cell layers within spleens which were immunized under optimal conditions. See Results, Section 3.3, sentence bridging columns 1 & 2. With regard to appellant's arguments regarding that spleen cells are not dendritic or antigen presenting cells, it is noted that consultation of an Immunology text (Fundamental Immunology by William Paul) indicates that the spleen contains a sufficient amount of antigen processing cells as the dendritic cells of the spleen process and present protein antigen effectively. Specifically, isolated (DCs) dendritic cells of the spleen have been found to be highly active as both stimulator cells in the MLR (mixed leukocyte reaction) and effective APCs (antigen presenting cells) in initiating CD8 cytotoxic responses in primary antibody responses and in presentation of antigens to CD4 T cells. See page 121, column 1, 2nd paragraph. Note that a copy of this page of the Text is provided to represent routine knowledge in the immunology art.

In response to appellant's arguments regarding the absence of a CTL response in the cited reference, Hui et al. report that the immunized spleen cells gave a 3-4 fold increase in the anti-H-$2k^b$ CTL response compared to non-immunized control mice. See page 154,

column 2, first paragraph, and Table 4. Note that the claims are not limited to a specific type of CTL response such that a CTL response upon restimulation *in vitro* is sufficient to meet the limitations of the claims. Hui et al. go on to report the transformation of animal tissue cell culture using the same apparatus. See page 154, column 2, first paragraph. Note that the claims are not limited to a specific antigen, or any particular route of administration by the biolistic approach.

Again, note that it is the Examiner's position that any effect of following the method steps of Hui et al. is inherent. As such, it is maintained that the methods of Hui et al. meet all of the limitations of the claims in that each and every step recited in the claims is taught by Hui et al., and any effect by following each step taught by Hui et al. is an inherent effect so long as there is no manipulative difference in the steps. Such inherency does not require a specific teaching of the intended effect by the cited references. Case law has established that in a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Thus, Hui et al. anticipate claims 1, 15, 29, and 68-71.

Note that the term "direct injection" is interpreted as encompassing both direct injection using a gene-gun as well as direct injection without use of a gene-gun. As such, Hui et al. meet the limitation "direct injection" in all of the claims included under this rejection, since Hui et al. teach direct injection into mouse spleen by use of a gene gun.

Therefore, for the reasons presented above and in the "Ground for Rejection", the Examiner maintains the rejection under 35 U.S.C. § 102.

As Applied to the Rejection Under 35 U.S.C. §103:

On page 9 of the Brief, appellant argues that a speculative one-sentence in Weiner as to a manner in which efficiency may be increased does not render obvious the present invention. In response, it is noted that the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Weiner et al. suggest applying particle bombardment to genetic immunization, and at the same time provides motivation to do so as it may increase efficiency of the immune response seen by use of direct injection into muscle. Further, the knowledge generally available to one of ordinary skill in the art is represented by the teachings of Tang or Barry, both of whom were already applying particle bombardment to genetic immunization.

On page 9 of the Brief, appellant argues that, contrary to the claimed methods, the methods of Weiner et al. appear to require the use bupivacaine along with the genetic vaccine for immunization of a host against a pathogen. In response, it is noted that the claimed

methods recite open claim language such as "which comprises" before the recitation of the claimed steps. As such, contrary to appellant's arguments that the claims recite delivery "without the use of bupivacaine", the present claims may encompass any agent, known at the time of the invention, which facilitates or promotes uptake of DNA by a cell.

On page 9 of the Brief, appellant argues that it is unclear as to whether Weiner is even targeting APCs. In response, it is noted that Weiner et al. discuss that the mechanism of action behind the immune response elicited by the target antigen involves antigen presentation which in turn stimulates CTL response. See column 8, lines 37-51. In fact, here, Weiner et al. report their observations that their genetic immunization protocol is more likely to elicit CTL response than other methods of immunization known in the art. See column 8, lines 48-51. Weiner et al. go on to report their results supporting a broader, more effective immune response which was capable, by virtue of CTL's, of completely eliminating tumors. See column 27, Example 2, lines 1-47. Note that Weiner et al. used tumor mouse models which did not involve intramuscular injection, as the tumor cells were transfected *ex vivo* and then implanted subcutaneously into the mouse model to show some level of protection against tumor growth by virtue of a CTL response. See Example 2. Appellant goes on the argue that, contrary to the claims, Weiner et al. discusses the aspect of integration of the DNA construct into the cell. However, at column 10, lines 59-62, Weiner et al. also discusses that the DNA may remain present in the cell as a functional extrachromosomal molecule. As such, appellant's argument is irrelevant, particularly since the teachings of Weiner et al. are not so

limited to integration of the DNA construct into the cell, and certainly embody wherein DNA may be introduced into the cells where it remains as a separate genetic material.

On page 9 of the Brief, appellant argues that Tang or Barry fails to overcome the shortcomings of the primary reference as Tang or Barry teach the use of particle bombardment only to elicit an antibody response, and not a response through the MHC class I pathway as required by the claims. In response, it is maintained that each of the cited references of record (Tang et al. and Barry et al.) teach each and every step of the claimed methods and thus, any effect, is an inherent to carrying out the method, so long as there is no manipulative difference in the steps. Such inherency does not require a specific teaching of the intended effect by the cited references. Case law has established that in a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). As such, both Tang et al. and Barry et al. teach a method identical to the claimed method, direct injection into the skin of a mouse by the biolistic approach a particle coated with DNA encoding an antigen of interest. As such, the generation of antibodies may have been the disclosed effect of Tang et al. and Barry et al., however, it is held that any other effect (APC presentation by MHC class I which is a CTL-mediated response) would have been inherent in following the steps of the methods taught by Tang et al. and Barry et al., as these steps are identical to the claimed steps, particularly since the production of antibodies is part of the cascade of immune responses as a result of activation of MHC class I. Reliance upon

inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

On page 9 of the Brief, appellant cites *In re Sernaker* to support that the combination of the prior art references must suggest an improvement along the lines of the invention to those skilled in the art. However, in response, it is noted that the combination of Weiner et al. taken with either Tang et al. or Barry et al. does, in fact, suggest an advantage to be derived from their combination. Weiner et al. suggests an increase in efficiency of the immune response seen over intramuscular injection of the genetic vaccine by use of the technique particle bombardment for administration of the genetic vaccine, the technique of which was available to the skilled artisan as represented by Tang and Barry. Furthermore, as to the suggestions taken from the cited prior art, it is not necessary that prior art suggest expressly, or in so many words, changes or possible improvements inventor made; it is only necessary that he apply knowledge clearly present in the prior art. *In re Sernaker*, 217 USPQ 1 (Fed. Cir. 1983). To this end, Weiner et al. suggest and provide motivation to their methods of genetic vaccination by applying the technique of particle bombardment, and such knowledge of performing the technique of particle bombardment, particularly as it pertains to genetic immunization, was clearly present in the prior art as represented by Tang et al. and Barry et al. It is not necessary for Weiner et al. to expressly suggest the precise manner of the increase of efficiency of the immune response as a result of the use of particle bombardment. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C.

§ 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Therefore, for the reasons presented above and in the "Ground for Rejection" the Examiner maintains the rejection under 35 U.S.C. § 103.

Conclusion:

In summary, it is considered that claims 1-3, 5-17, 19-32, 34-47, 49-61, and 63-71, on appeal, are not enabled by the specification for the claimed breadth, are anticipated and obvious over the cited prior art of record, and appellant's arguments and evidence fail to persuade otherwise. For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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